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Datasheet for the decision of 14 May 2019

Case Number: T 0563/15 - 3.3.01

Application Number: 08730508.2

Publication Number: 2114423

IPC: A61K35/74, A61K31/202, A61P29/00

Language of the proceedings: EN

Title of invention:
PRODUCT CONTAINING INACTIVATED PROBIOTIC FOR INFANTS

Patent Proprietor:
MJN U.S. Holdings LLC

Opponent:
Nestec S.A.

Relevant legal provisions:
EPC Art. 123(2), 84, 83, 54, 56
RPBA Art. 13(1), 12(4)

Keyword:

Amendments - added subject-matter (no)
Claims - clarity (yes)
Sufficiency of disclosure - (yes)
Novelty - (yes)
Inventive step - (yes)
Late-filed facts - admitted (yes)

Decisions cited:

G 0003/14, G 0005/83

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Case Number: T 0563/15 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 14 May 2019

Appellant: (Opponent)	Nestec S.A. Avenue Nestlé 55 1800 Vevey (CH)
Representative:	Rupp, Christian Mitscherlich PartmbB Patent- und Rechtsanwälte Sonnenstraße 33 80331 München (DE)
Respondent: (Patent Proprietor)	MJN U.S. Holdings LLC 225 North Canal Street 25th Floor Chicago, Illinois 60606 (US)
Representative:	Cawdell, Karen Teresa Reckitt Benckiser, Corporate Services Limited Legal Department - Patents Group Dansom Lane Hull HU8 7DS (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 16 January 2015 concerning maintenance of the European Patent No. 2114423 in amended form.**

Composition of the Board:

Chairman A. Lindner
Members: R. Hauss
M. Blasi

Summary of Facts and Submissions

I. European patent No. 2 114 423 (the patent in suit) was granted with a set of 22 claims. The independent claims read as follows:

"1. A nutritional composition for use in treating, preventing or reducing systemic inflammation in an infant, wherein the nutritional composition comprises heat inactivated *Lactobacillus rhamnosus* GG and is to be administered in an amount effective to provide between $1x10^4$ and $1x10^{10}$ cell equivalents of inactivated *Lactobacillus rhamnosus* GG per kg body weight per day to the infant."

"12. Use of heat inactivated *Lactobacillus rhamnosus* GG for the manufacture of a nutritional composition for the treatment, prevention or reduction of systemic inflammation in an infant, wherein the nutritional composition is to be administered in an amount effective to provide between $1x10^4$ and $1x10^{10}$ cell equivalents of inactivated *Lactobacillus rhamnosus* GG per kg body weight per day to the infant."

The remaining claims 2 to 11 and 13 to 22 are dependent claims. Claims 2 and 13 read as follows:

"2. The nutritional composition for use of claim 1, which further comprises at least one prebiotic."

"13. The use of claim 12, wherein the nutritional composition further comprises at least one prebiotic."

In the description of the patent in suit, the abbreviation **"LGG"** is used to designate *Lactobacillus rhamnosus* GG.

II. The patent in suit was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was insufficiently disclosed and extended beyond the content of the application as filed.

III. In the course of the opposition proceedings, the patent proprietor submitted claims of an amended main request (filed with a letter dated 20 November 2013) and, with a later submission of 3 November 2014, a further set of claims entitled "1st Auxiliary Request".

While the independent claims (claims 1 and 12) of the **new main request** are identical to claims 1 and 12 as granted, certain dependent claims were modified. Claims 2 and 13 correspond to claims 2 and 13 of the patent in suit (see point I above), except that they contain the additional restriction: "and wherein the infant is a formula-fed infant".

IV. The documents cited in the opposition and appeal proceedings included the following:

D1: J. Nutr. 135, 1752-1756 (2005)
D4: US 2006/0233752 A1
D11: US 2005/0180962 A1
D29: J. Nutr. 134, 1964-1969 (2004)
D31: JPGN 36, 223-227 (2003)
D33: JPGN 42, 545-552 (2006)
D33A: Gastroenterology 126, 1358-1373 (2004)

V. The decision under appeal is the interlocutory decision of the opposition division, announced on 4 December 2014 and posted on 16 January 2015, finding that the patent as amended in the form of the main request of 20 November 2013 met the requirements of the EPC.

VI. According to the decision under appeal:

(a) The opposition division did not admit document D33 (filed by the patent proprietor on 4 December 2014) into the proceedings since it had not been submitted in due time and was not of particular relevance (Article 114(2) and Rule 116(1) EPC).

(b) With regard to combinations of the technical features "nutritional composition", "infant formula", "formula-fed infant" and "comprises at least one prebiotic" objected to by the opponent, the claims according to the main request did not define added subject-matter (Article 123(2) EPC).

(c) There was no contradiction between the terms "formula-fed infant" used in dependent claims 2 and 13 and "nutritional composition" used in claim 1 (Article 84 EPC).

(d) The disclosure pertaining to the invention defined in the claims of the main request was sufficient, since the therapeutic indication was rendered credible by the data shown in example 1 of the patent in suit, and the term "cell equivalents" would be readily understood in view of the context provided (Article 83 EPC).

(e) The claimed subject-matter was novel relative to the disclosure of, *inter alia*, document D11, which did not directly and unambiguously disclose heat-inactivated LGG, let alone in the specific context of the treatment of systemic inflammation in infants (Articles 52(1) and 54 EPC).

(f) Document D4 was regarded as the closest prior art. The claimed subject-matter differed from the disclosure of D4 in the use of heat-inactivated

instead of viable LGG. In view of the data presented in example 1 of the patent in suit, the technical problem to be solved was the provision of an improved composition for treating, preventing or reducing systemic inflammation in an infant. The prior art on file would not have led the way to the claimed subject-matter. In particular, document D31 taught away from orally administering inactivated LGG to infants. The subject-matter of the main request therefore involved an inventive step (Articles 52(1) and 56 EPC).

VII. The opponent (appellant) filed an appeal against that decision, requesting the revocation of the patent.

VIII. With its reply to the statement setting out the grounds of appeal, the patent proprietor (respondent) maintained its main request and its first auxiliary request (see point III above), filed three amended sets of claims as auxiliary requests 2 to 4 and re-submitted document D33.

IX. Oral proceedings before the board, as requested by both parties, took place on 14 May 2019.

X. The appellant's arguments relating to the respondent's main request may be summarised as follows:

Amendments (Article 123(2) EPC)

The term "nutritional composition" employed in claims 1 and 12 was an inadmissible generalisation of the term "children's or infant's product" employed in claim 1 of the application as filed.

Furthermore, several selections from the content of the application as filed were required to arrive at the combination of technical features defined in

claims 1 and 12, namely, the selection of infants as the target group, systemic inflammation as the health problem to be addressed, LGG as the probiotic (by first selecting the genus *Lactobacillus* and then selecting the specific *Lactobacillus* strain) and heat as the means of inactivation.

The combination of the feature in claims 2 and 13 specifying that the infant was a formula-fed infant with the feature from claims 1 and 12 relating specifically to heat-inactivated LGG (rather than to an inactivated probiotic in general) also extended beyond the content of the application as filed.

Clarity (Article 84 EPC)

The term "nutritional composition" employed in claims 1 and 12 covered any nutritional product (including those not addressing the nutritional requirements of infants), whereas the more specific term "formula-fed infant" employed in dependent claims 2 and 13 related to an infant receiving a substitute for human milk satisfying the infant's nutrient requirements. This gave rise to a discrepancy between the dependent and independent claims.

Sufficiency of disclosure (Article 83 EPC)

The meaning of the undefined term "cell equivalents of inactivated *Lactobacillus rhamnosus* GG" used in the independent claims was so obscure that the person skilled in the art would not be able, on that basis, to put the claimed subject-matter into practice. Since it was well known that the term "cfu", which stands for "colony-forming units", did not necessarily refer to single cells, it could not be simply assumed that "cell equivalents" corresponded to, or were even correlated with, inactivated cfu. The measurement units

indicated for the two parameters were not identical, since the relevant text passage in paragraph [0107] of the patent in suit mentioned a concentration of viable bacteria ("$1x10^8$ cfu/L per kg body weight per day of viable LGG") as opposed to an amount of inactivated bacteria ("$1x10^8$ cell equivalents per kg body weight per day of inactivated LGG"). Owing to these discrepancies, the skilled person reading the patent in suit would not conclude that an amount of viable bacteria in terms of cfu corresponded to the same amount of inactivated bacteria in terms of cell equivalents. Moreover, it was not clear how cell fragments generated by heat inactivation should be taken into account.

According to a further objection, the data provided in the patent in suit did not render the claimed therapeutic benefit credible. Data obtained with a rat infant model could not be extrapolated to human infants because the bacteria populations in the gut were different - as corroborated by the teaching of document D31 with respect to an adverse effect observed in human infants. In any case, therapeutic efficacy had not been rendered credible with regard to the lower part of the dosage range and all conceivable methods of heat inactivation (as confirmed by D31: page 226, first paragraph, teaching that the generation of heat shock proteins might have unfavourable effects).

Novelty (Articles 52(1) and 54(1)-(2) EPC)

The subject-matter of independent claims 1 and 12 of the main request lacked novelty relative to the disclosure of document D11, which described all the features of claims 1 and 12. There could be no doubt that the term "L. GG" mentioned in paragraph [0046] of document D11 referred to *Lactobacillus rhamnosus* GG.

Admission of new lines of argument

Documents D31 and D33 had both been introduced into the proceedings by the respondent, and the appellant's assessment of inventive step starting from either D31 or D33 had been presented in direct response to the respondent's arguments and to the reasoning given in the decision under appeal.

Inventive step (Articles 52(1) and 56 EPC)

Example 1 of the patent in suit did not demonstrate the therapeutic efficacy of LGG with regard to systemic inflammation because the same level of improvement was not observed in all distal organs examined. Moreover, it was uncertain which dosage of viable LGG had actually been administered since the unit "cfu/L per kg body weight per day" seemed to refer to a concentration rather than an amount. For this reason, the dosage could not be compared directly to the amount of inactivated LGG administered (indicated as "cell equivalents per kg body weight per day"). Thus, no valid conclusion could be obtained from the information presented in example 1, let alone a confirmation of the allegedly improved efficacy of heat-inactivated LGG.

Each of documents D4, D31 or D33 was a possible starting point for the assessment of inventive step.

Starting from documents D4 or D33 (both relating to the administration of viable LGG), the person skilled in the art seeking to provide alternative compositions would routinely investigate further forms of LGG, including non-viable forms. In addition, document D33 mentioned that the benefits of heat-killed probiotics remained under investigation (D33: page 551, column 1, lines 28 to 30). Supplementary documents D1, D11 and D29 also pointed the skilled person to heat-inactivated

non-viable LGG. Contrary to the respondent's view, the experimental models relied on in documents D1 (an *in vitro* cell model) and D29 (young adult rats) were equally valid for adult and infant cells since cell lines were identical in adults and infants.

Document D31 described a study aimed at assessing the efficacy of heat-inactivated LGG in the treatment of atopic eczema, which was a systemic inflammation, in infants. Since it had not been shown that inactivated LGG provided a statistically significantly better efficacy than viable LGG, the objective technical problem could be defined as the provision of an alternative probiotic, compared to the administration of viable LGG, in the treatment of systemic inflammation in an infant. Document D31 itself, irrespective of an adverse effect (diarrhoea) observed in a number of patients, nevertheless demonstrated a therapeutic benefit of heat-inactivated LGG. While the document contained both positive and negative pointers, it did not establish a technical prejudice against the administration of heat-inactivated LGG to infants. Nor had it been shown in the patent in suit that the alleged prejudice or disincentive had been overcome rather than simply ignored, since the rat model relied on according to example 1 was not suitable to show that intestinal discomfort was avoided with the claimed nutritional composition.

XI. The respondent's arguments in defence of its main request may be summarised as follows:

Amendments (Article 123(2) EPC)

Adequate support for the definition of claims 1, 2, 12 and 13 of the main request was found in claims 1 and 12

and paragraphs [0069] and [0074] of the application as filed.

Clarity (Article 84 EPC)

The term "formula-fed infant" employed in claims 2 and 13 defined an infant that was at least partially fed with formula milk. This meaning was not in conflict with the infant also ingesting a further nutritional composition or the embodiment according to which the nutritional composition itself was a formula milk.

Sufficiency of disclosure (Article 83 EPC)

The person skilled in the art would readily appreciate in the given context that the term "cfu" (colony-forming units) referred to viable bacteria and the term "cell equivalents" to a corresponding quantity of inactivated bacteria.

The teaching of document D31, which in any case disclosed a different dosage of probiotic bacteria, did not invalidate the data presented in example 1 of the patent in suit. These *in vivo* data, obtained with a well-established infant rat model known to be predictive for systemic inflammation, demonstrated that the levels of several pro-inflammatory cytokines (which were markers of inflammation) were reduced upon administration of LGG, in particular heat-inactivated LGG. Document D33, which relied on the same infant rat model as the patent in suit and document D4, was cited as evidence that the infant rat model was well established in the relevant art (the first author of D33 being an expert of the appellant).

The appellant had not provided reasoned serious doubts substantiated by verifiable facts in support of its

allegation that there might be certain dosages or certain heat activation methods which did not work.

Novelty (Articles 52(1) and 54(1)-(2) EPC)

The combination of features defined in independent claims 1 and 12 was not specifically disclosed in document D11. In particular, D11 did not define a daily dosage of probiotic bacteria. Multiple selections were necessary to combine the further technical features required.

Admission of new lines of argument

The appellant's lines of argument starting the assessment of inventive step either from document D31 or from document D33 amounted to a fresh case introduced for the first time during the appeal proceedings and should therefore be held inadmissible.

Main request - inventive step (Article 56 EPC)

Document D4 was the most suitable starting point for the assessment of inventive step. Starting from the technical teaching of D4, the objective technical problem to be solved was the provision of a nutritional composition for use in treating, preventing or reducing systemic inflammation in an infant having an improved effect on systemic inflammation compared with the prior art. There was no indication in documents D4, D33, D1, D11 or D29 that the effect of LGG on systemic inflammation could be improved by heat inactivation, as shown in example 1 of the patent in suit.

Document D31 taught away from the invention, since - owing to an adverse effect (diarrhoea)- it called the use of heat-inactivated LGG for infant therapy into question.

Document D33 was a scientific article corresponding to US patent application D4. Since the content of these documents was essentially identical, D33 was not more relevant than D4.

XII. The appellant requested that the decision under appeal be set aside and that European patent No. 2 114 423 (the patent in suit) be revoked.

Within the purview of that request, the appellant furthermore requested that auxiliary requests 2, 3 and 4 and documents D36 and D37 (submitted by the respondent with a letter dated 4 April 2017) not be admitted into the appeal proceedings.

XIII. The respondent requested that the appeal be dismissed, or, in case the decision under appeal was set aside, that the patent be maintained in amended form with the claims of auxiliary request 1 filed with the letter dated 3 November 2014, or in the alternative, with the claims of one of auxiliary requests 2, 3 and 4, all filed with the reply to the statement setting out the grounds of appeal.

Furthermore, the respondent objected to the appellant's using documents D33 or D31 as the starting point for the assessment of inventive step.

Reasons for the Decision

1. Amendments (Article 123(2) EPC)

1.1 Claims 1 and 12

1.1.1 Claim 1 of the application as filed (published as WO 2008/106373) is directed to a "children's or infant's *[sic]* product comprising at least one inactivated probiotic, wherein the product is formulated to deliver from between about $1x10^4$ to about $1x10^{10}$ cell equivalents of inactivated probiotic per kg body weight per day to a child or infant (...)".

1.1.2 Since the target group of the further medical use according to claims 1 and 12 of the present main request is infants (mentioned twice in each claim; see point I above), it is implicit that the "nutritional composition" of claims 1 and 12 must be suitable for the nutrition of infants.

This is in conformity with claim 1 of the application as filed, which defines an "infant's" (or presumably, infants') product. It is also readily apparent throughout the text of the application as filed (see, for instance, paragraphs [0059], [0060] and [0069]) that the envisaged product is to be ingested.

Hence, the use of the term "nutritional composition" in present claims 1 and 12 does not introduce subject-matter extending beyond the content of the application as filed.

1.1.3 Infants are one of only two alternative target groups envisaged in claim 1 of the application as filed. Infants are furthermore separately disclosed in paragraphs [0058] ("In some embodiments, the subject

is an infant.") and [0069] ("In other embodiments, the product may be an infant's nutritional product"). Thus, infants are presented as a distinct general embodiment in the application as filed and the restriction to infants as the target group in present claims 1 and 12 does not introduce added subject-matter. Formula-fed infants are specifically mentioned in paragraphs [0095] and [0096] (see paragraph [0095]: "In an embodiment of the present invention, the subject is a formula-fed infant.").

1.1.4 The use of the composition in preventing, treating or reducing systemic inflammation is also mentioned in the application as filed in the form of a general disclosure, namely, in paragraphs [0093] to [0096] (e.g. paragraph [0093]: "In some embodiments of the present invention, the subject is in need of the treatment, reduction, or prevention of systemic inflammation"). It is moreover explicitly envisaged for infants (see paragraph [0094]: "In certain embodiments, the inactivated probiotic may be administered to an infant or child to prevent, treat or reduce systemic inflammation"). Finally, the dosage range recited in claim 1 as filed is disclosed in the description as the "amount sufficient to reduce or prevent systemic inflammation in a subject" (see paragraph [0067] of the application as filed).

1.1.5 The embodiment using inactivated *Lactobacillus rhamnosus* GG (LGG) as the inactivated probiotic is directly disclosed in the application as filed (see paragraph [0062]: "As set forth above, in a particular embodiment of the invention the inactivated probiotic may be LGG"). It is, moreover, the only embodiment illustrated in the examples.

1.1.6 Thus, the administration of inactivated LGG to infants for the therapeutic indication "systemic inflammation" was envisaged and is supported by general disclosures in the application as filed.

1.1.7 Only one selection is therefore required to arrive at the subject-matter of claims 1 and 12 of the present main request, namely, the selection of heat treatment among other inactivation methods proposed according to paragraph [0068] of the application as filed ("In the present invention, at least one probiotic that has been inactivated is utilized. Inactivation may occur through any method currently known in the art or yet to be developed. The inactivation may be accomplished, for example, via heat treatment, lyophilization, ultraviolet light, gamma radiation, pressure, chemical disruption, or mechanical disruption.").

1.2 Claims 2 and 13

The embodiment according to claims 2 and 13 of the present main request finds support in the application as filed in paragraph [0074], which specifically discloses that the inactivated probiotic may be combined with one or more prebiotics to treat or prevent systemic or respiratory inflammation in formula-fed infants.

1.3 For these reasons, claims 1, 2, 12 and 13 of the main request do not contain subject-matter extending beyond the content of the application as filed.

2. Clarity (Article 84 EPC)

2.1 Claims 2 and 13 of the present main request differ from the corresponding claims 2 and 13 of the patent in suit by the additional restriction: "and wherein the infant is a formula-fed infant", which is not mentioned anywhere in the granted set of claims.

2.2 Contrary to the appellant's view, the combination (by back-reference of dependent claims 2 and 13 to the independent claims 1 and 12) of the features "nutritional composition" and "formula-fed infant" does not give rise to a discrepancy:

- As explained above (see points 1.1.2 and 1.1.3), the nutritional composition defined in the independent claims is restricted to a composition suitable for the nutrition of infants, owing to the explicit presence, in both claims, of the features "in an infant" and "to be administered ... to the infant".

- The further requirement introduced in claims 2 and 13 that the infants are formula-fed infants does not result in a contradiction or discrepancy. As previously pointed out by the opposition division in the decision under appeal (Reasons: 16), the term "formula-fed infant" is normally understood to refer to infants which are at least partially fed with formula milk. As set out in paragraphs [0070] and [0071] of the patent in suit, the nutritional composition according to the present claims may be some kind of supplement or it may itself be an infant formula. Both options are entirely consistent and compatible with the envisaged administration to formula-fed infants.

2.3 Hence, the meaning of claims 2 and 13 is clear.

3. Sufficiency of disclosure (Article 83 EPC)

3.1 Dosage to be administered

3.1.1 According to the independent claims of the main request, the nutritional composition is to be administered in an amount effective to provide between $1x10^4$ and $1x10^{10}$ cell equivalents of inactivated LGG per kg body weight per day to the infants.

3.1.2 The appellant contended that the person skilled in the art reading the patent in suit would be unable to establish what was meant by the term "cell equivalents", which was not defined in the patent and, by all appearances, was not correlated to the "cfu" unit conventionally used for viable bacteria. Still according to the appellant, since the dosage was furthermore indicated as an effective amount and only in relation to the intended use, the person skilled in the art would be unable to determine the actually required concentration or amount of LGG in the nutritional composition.

3.1.3 The board does not reach the same conclusions, for the following reasons:

(a) "Cfu" (colony-forming units) is a known parameter commonly used to estimate the number of viable bacteria cells in a sample based on their ability to give rise to colonies under specified conditions. When counting colonies, it is indeed uncertain if the colony arose from one cell or a group of cells. However, in view of points (e) to (g) below, this is not crucial.

(b) In the patent in suit, the term "cfu" is employed to indicate a quantity of viable bacteria (see paragraphs [0074] and [0107]), while the term "cell equivalents" is used for a quantity of inactivated

bacteria (see paragraphs [0068] and [0107] and claims 1 and 12).

(c) According to example 1 (see paragraph [0107]), one of the groups of the animal study described (which was carried out with neonatal rat pups):

"was given a supplement of $1x10^8$ cell equivalents per kg body weight per day of inactivated LGG. (...) A second group was given a supplement of $1x10^8$ cfu/L per kg body weight per day of viable LGG".

(d) Since this passage supposedly indicates daily dosages, the measurement unit should refer to an amount of bacteria delivered per kg body weight per day. Hence, it is immediately apparent to the reader that the unit indicated in paragraph [0107] for viable LGG is not plausible and must contain an error - since it convolutes a concentration (cfu/L) with a dosage (cfu per kg body weight per day). It is equally evident that the unit should correctly read "cfu per kg body weight per day", as corroborated in paragraph [0074] of the description, where this unit is indeed used to indicate dosage ranges of viable bacteria.

(e) In the absence of a different definition of the term, the person skilled in the art would infer from the context provided in the patent in suit that "cell equivalents" is simply a name used to replace the term "cfu" after inactivation of the bacterial cells (since inactivated bacteria are no longer able to form colonies and the term "cfu" is therefore no longer appropriate). The common-sense approach would be to first determine an amount of viable bacteria (in terms of the well-known parameter "cfu") and then to apply an inactivation

method, after which the term "cfu" will simply be replaced by the term "cell equivalents", the actual amount of material being unchanged. Thus, the skilled person would infer that paragraph [0107] indeed relates to corresponding dosages of viable and inactivated cell material, which is also the most logical comparison for the purposes of a comparative study such as presented in example 1.

(f) The passage in example 2, paragraph [0122], of the patent in suit supports this interpretation, since it mentions, in the context of an *in vitro* test, that intestinal epithelial cells were pretreated with a concentration of "viable or UV-inactivated LGG at $1x10^8$ cfu/L". This evidently relates to the same material and concentration before and after inactivation (irrespective of the fact that "cfu" was, presumably due to an oversight, not replaced by "cell equivalents" in the case of the inactivated material).

(g) The appellant's assertion that the term "cell equivalents" must refer to solitary inactivated cells (rather than groups of cells), and therefore is not correlated to the "cfu" unit, appears far-fetched and is based solely on a particular literal interpretation of the words "cell equivalents" rather than on any specific pertinent information or instruction found in the patent.

(h) Based on the dosage range specified in claims 1 and 12 (and where applicable, by taking typical serving sizes into account), the skilled person would also be able to determine, without any difficulty, concentrations of heat-inactivated LGG in a given product type suitable for providing an infant with a daily dosage in the required range.

3.1.4 In conclusion, the person skilled in the art would understand the meaning of the term "cell equivalents" (see point (e) above) and would also be able to manufacture a nutritional composition providing the indicated dosage of inactivated LGG.

3.2 Credibility of the therapeutic indication

3.2.1 Content of example 1

Example 1 of the patent in suit relates to an animal study carried out with heat-inactivated LGG, while example 2 relates to *in vitro* tests employing UV-inactivated LGG material. Since the present claims are restricted to heat-inactivated LGG, only the inactivated material of example 1 corresponds to the definition in the claims.

The study reported in example 1 relies on an *in vivo* infant rat model in which a pro-inflammatory response (systemic inflammation) can be induced by *Escherichia coli* lipopolysaccharide (abbreviated as "LPS").

The study was carried out with four gastrostomy feeding groups of infant rats fed with rat milk substitute: an LPS plus heat-inactivated LGG group (in conformity with claims 1 and 12), an LPS plus viable LGG group, an LPS group and a control group receiving neither LPS nor LGG. Mother-reared rats of the same age were used as reference controls.

According to the data presented in example 1, the levels of certain LPS-induced pro-inflammatory cytokines in the liver, lung and plasma were reduced upon administration of LGG, and in particular inactivated LGG. As these cytokines are markers of inflammation, it may be concluded that inactivated LGG can produce anti-inflammatory effects.

3.2.2 Suitability of the rat model according to example 1 of the patent in suit

(a) The presumption in such a case must be that the person skilled in the art would use an animal model which is indeed suitable for representing systemic inflammation in human infants.

(b) In the present case, this presumption is strengthened by the fact that the same rat model was used in the prior art (documents D4, D33).

(c) The appellant argued in this context that data obtained with rats could not be extrapolated to humans since the immune systems and bacteria populations in the gut were different. According to the appellant, this argument was corroborated by the teaching of document D31 which demonstrated that a gastrointestinal adverse effect (diarrhoea) was observed in human infants upon the administration of heat-inactivated LGG.

(d) However, the appellant's argument here is speculative and not supported by any verifiable data about relevant differences in the bacteria populations and immune systems.

(e) Document D31 relates to a clinical study which had the aim of assessing the efficacy of oral supplementation with viable or heat-inactivated probiotic bacteria in the management of atopic disease (see D31: abstract). D31 presents data obtained with a study population of 35 human infants, involving a mean intake of 3×10^{10} cfu of viable LGG, or a corresponding dosage of heat-inactivated LGG, per kg body weight and presumably per day. Since this mean intake is higher than the upper limit of 1×10^{10} cell equivalents defined

in claims 1 and 12, it cannot be inferred that the data reported in D31 are representative of the dosage range defined in the present claims, (irrespective of the - unproven - possibility that in some instances individual daily intakes may have been below 1 x 10^{10} cell equivalents per kg).

(f) For these reasons, neither the appellant's general considerations regarding potential differences in bacteria populations and immune systems nor the specific data reported in D31 invalidate the *in vivo* results reported in example 1 of the patent in suit.

3.2.3 Sufficiency of disclosure over the entire scope claimed

The appellant's argument that therapeutic efficacy was not achievable over the entire scope of the treatment as defined in the claims was not supported by any evidence or theoretical considerations going beyond mere speculation.

As set out in points 3.2.1 and 3.2.2 above, the therapeutic indication (treating, preventing or reducing systemic inflammation in an infant) is supported by experimental data presented in example 1.

An objection of insufficiency of disclosure presupposes the existence of serious doubts substantiated by verifiable facts.

The appellant did not present any experimental data in support of its allegation that there might be certain heat-inactivation methods, or certain dosages covered by the claims, which might not work to provide the desired therapeutic benefit.

As far as theoretical considerations are concerned, while it might be hypothesised that low dosages might

not be effective, or that particularly destructive heat-inactivation techniques might affect efficacy, these speculations about the potential non-availability of particular variants do not amount to a serious doubt that the desired therapeutic benefit would not be obtained across most or all of the scope claimed.

Moreover, even if the person skilled in the art encountered practical difficulties of that nature, they would not be at a loss for obvious counter-measures such as increasing the dosage or using less destructive inactivation techniques. With regard to the second point, the patent in suit expressly mentions, e.g. in paragraph [0028], that the cellular components of the inactivated probiotic should "retain the same or similar biological reactive *[sic]* attributes as those of the viable or non-inactivated cells", thus pointing the reader to inactivation methods using mild conditions.

Rather than to (in)sufficiency of disclosure within the meaning of Article 83 EPC, this aspect of the appellant's objections therefore relates to a mere hypothetical uncertainty about the precise boundaries of the scope defining effective inactivation methods and dosages. Thus, it amounts to an objection regarding a lack of clarity pursuant to Article 84 EPC. Since the technical features in question (i.e. the dosage range and the feature relating to heat inactivation) were already present in the claims as granted, this issue is not within the scope of opposition appeal proceedings (see Enlarged Board decision G 3/14, OJ EPO 2015, A102).

3.3 For these reasons, the claimed subject-matter is disclosed in the patent in suit in a manner sufficiently clear and complete for it to be carried

out by a person skilled in the art, in accordance with Article 83 EPC.

4. Novelty (Articles 52(1) and 54(1)-(2) EPC)

4.1 Document D11 relates to enteral formulations containing inactivated probiotic bacteria. In one embodiment, the inactivation method is pasteurisation (see D11: claim 2 and paragraph [0057]); however, other inactivation methods not involving heat treatment are also envisaged (see D11: paragraphs [0051] to [0056]).

4.2 D11 is a US patent application with 40 claims and 260 paragraphs of description. In this document, *Lactobacillus rhamnosus* is mentioned only once, as "*L. rhamnosus*", in a long list of suitable probiotic bacteria which includes *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Leuconostoc* and several other bacteria species (see D11: paragraph [0046]). The same paragraph contains the only mention in D11 of *"L. GG"*, which occurs between *"L. cellobiosus"* and *"L. gasseri"* without further explanation of the meaning of "*L. GG*".

Infants are mentioned only once, in a different passage (see paragraph [0042]), as a possible target group.

The formulations according to D11 are intended for treating "any disorder amenable to treatment with viable probiotic bacteria", which is not limited to disorders involving systemic inflammation (see D11: paragraphs [0015] to [0019] and [0039]).

Moreover, D11 does not indicate a daily dosage to be administered relative to a patient's body weight. In this context, it should also be noted that one dosage unit is not necessarily identical to the recommended daily dose. While it is mentioned in D11 (see paragraphs [0013] and [0062]) that the

formulations may contain from about 1 x 10^5 to about 1 x 10^{14} bacteria per dosage unit (or amounts within various narrower ranges encompassed by this largest range), this does not amount to an unambiguous disclosure of a dosage between 1 x 10^4 and 1 x 10^{10} cell equivalents per kg body weight per day, as specified in claims 1 and 12 of the main request.

4.3 Hence, even assuming in the appellant's favour that the term *"L. GG"* indeed relates to *Lactobacillus rhamnosus* GG, the further mandatory technical features of claims 1 and 12 defining the therapeutic indication, patient group and dosage are not disclosed in D11 in direct and unambiguous combination with *Lactobacillus rhamnosus* (let alone *Lactobacillus rhamnosus* GG) inactivated by heat treatment such as pasteurisation.

4.4 For these reasons, the subject-matter of claims 1 and 12 is novel relative to the disclosure of document D11.

5. Inventive step (Articles 52(1) and 56 EPC)

Patent in suit

5.1 The patent in suit (see paragraph [0027]) seeks to provide a non-viable supplement of beneficial probiotic bacteria that may treat or prevent systemic inflammation in infants. It is expected that a non-viable alternative to viable probiotics may pose a lower risk of infection or interaction with other food components and may have a longer shelf life.

5.2 Claims 1 and 12 according to the main request relate to a further medical use involving a nutritional composition containing heat-inactivated LGG which is to be used for the treatment, prevention or reduction of systemic inflammation in an infant.

Claim 1 is a purpose-related product claim in the format according to Article 54(5) EPC, while claim 12 is drafted in the so-called Swiss-type format (see Enlarged Board decision G 5/83, OJ EPO 3/1985, 64).

Starting point in the prior art

5.3 Document D4

5.3.1 It was common ground that document D4 was suitable as a starting point for the assessment of inventive step.

5.3.2 D4 relates to a method for treating, preventing or reducing systemic inflammation in a formula-fed infant. This method involves the administration of viable LGG to the infant (see D4: claim 1, paragraphs [0030], [0051] to [0055], [0068] to [0069], examples).
D4 presents experimental data obtained with the same infant rat model employed according to the patent in suit. In paragraph [0023], D4 emphasises that there are large and fundamental differences between the infant gut and immune system compared to those of an adult and therefore, studies that focus on adult subjects or adult cell lines are not useful for evaluating the effect of LGG on infants.

5.4 Document D33

5.4.1 In an alternative approach, the appellant proposed that the assessment of inventive step should be carried out starting from the technical teaching of document D33.

5.4.2 According to D33, a gastrostomy-fed rat infant "pup-in-a-cup" model was used to test the hypothesis that enterally administered LGG decreased the pro-inflammatory response induced by LPS in the developing infant rats' small intestine, plasma, lung and liver. It was found that LGG provided by the enteral route

was able to downregulate LPS-induced pro-inflammatory mediators (see D33: Abstract).

5.4.3 Admission of the new line of argument

With its reply to the statement setting out the grounds of appeal, the respondent re-submitted document D33, previously presented but not admitted during oral proceedings before the opposition division (see point VI.(a) above).

In response, the appellant argued that D33 was similar in its content to D4 and therefore, if admitted into the proceedings by the board, was likewise suitable as the starting point in the prior art for the assessment of inventive step (see the appellant's letter dated 21 July 2016, 8.2.b)).

The appellant's introduction of this line of argument was thus occasioned by the respondent's re-submission of D33 and, since the content of D33 is very similar to that of D4 regarded as the closest prior art in the decision under appeal (see D33: Abstract, Discussion), it does not give rise to any new issues amounting to a "fresh case".

Under these circumstances, the board found it appropriate to admit the appellant's new line of argument which relies on D33 as the starting point for the assessment of inventive step (Article 13(1) RPBA).

5.5 Document D31

5.5.1 According to yet another approach, the appellant proposed that the assessment of inventive step should start from the technical teaching of document D31.

5.5.2 Document D31 is a scientific article which presents data obtained with human infants who received oral

supplementation of viable and heat-inactivated LGG (see point 3.2.2(e) above).

5.5.3 Admission of the new line of argument

This line of argument was presented for the first time in the statement setting out the grounds of appeal, in conformity with the requirements of Article 12(1) and (2) RPBA. The respondent contended that this line of argument should have been presented during the proceedings before the opposition division and therefore should not be admitted pursuant to Article 12(4) RPBA.

Document D31 was first introduced by the respondent, with its reply to the notice of opposition. The discussion in the opposition proceedings subsequently focused on whether D31, as a supplementary document, taught away from the claimed subject-matter (as argued by the respondent).

This is still the main issue to be discussed if D31 is to be used as the starting point for the assessment of inventive step rather than as a supplementary document. The board cannot therefore recognise a major shift or increase in complexity in the appellant's case (see, for instance, the appellant's letter of 23 June 2014, VII-5).

In the present circumstances, the introduction of the additional inventive-step approach can be regarded as a normal and legitimate reaction of a losing party to the outcome of the proceedings before the opposition division, thus attempting to complete and improve its case.

Since the respondent presented its objection only at a very late stage of the appeal proceedings (namely on the day of the oral proceedings before the board)

and did not specify why the new inventive-step approach ought to have been filed at any particular point during the proceedings before the opposition division, the board saw no compelling reason for not admitting the new line of argument (Article 12(4) RPBA).

Technical problem starting from D4 and solution

5.6 The subject-matter of claims 1 and 12 differs from the disclosure of D4 in that heat-inactivated instead of viable LGG are to be administered.

5.7 The technical effect resulting from this difference is apparent from example 1 in combination with figures 1 to 6 of the patent in suit.

5.7.1 As already mentioned (see point 3.2.2 above), the appellant did not succeed in substantiating the alleged doubts concerning the suitability of the infant rat model used according to example 1 of the patent in suit.

5.7.2 According to the experimental data obtained with the help of that animal model, the anti-inflammatory effect of heat-inactivated LGG was found to be more pronounced than that of viable LGG, as indicated by cytokine levels observed in the plasma and liver. The anti-inflammatory effect in the lungs was similar to that of viable LGG.

5.7.3 The appellant argued that the effect of heat-inactivated LGG was only local and not systemic (as no effect had been shown in the lungs). The board does not reach the same conclusion, since an anti-inflammatory effect of heat-inactivated LGG was also observed in the lungs (although this effect was not more pronounced than that attained with viable LGG).

5.7.4 Thus, the experimental data presented in the patent in suit render it credible that the administration of heat-inactivated LGG acts on systemic inflammation by providing a systemic effect which is more pronounced in certain organs than that of viable LGG (see the decision under appeal, point 18.1).

5.7.5 It is also credible in view of common general knowledge that a product containing inactivated instead of viable bacteria may present advantages with regard to required storage conditions and shelf life.

5.8 Starting from the technical teaching of document D4, the technical problem to be solved is thus the provision of an improved probiotic nutritional composition for use in treating, preventing or reducing systemic inflammation in an infant.

5.9 The solution to this problem is as defined in claims 1 and 12 of the main request.

Obviousness of the solution

5.10 As acknowledged in the patent in suit (see paragraph [0027]), active or viable probiotics are sensitive to heat, moisture and light, and ideally should be refrigerated to maintain viability. If it were indeed confirmed that the claimed subject-matter achieved an improvement in terms of more favourable storage properties of the nutritional composition (see point 5.7.5 above), such an effect could not be considered as unexpected in view of common general knowledge. Thus, the alleged improvement in storage properties cannot contribute to the inventiveness of the claimed subject-matter.

5.11 On the other hand, the observed improvement in therapeutic benefit in respect of a more pronounced

effect on systemic inflammation in certain organs (see point 5.7.4 above) could not have been derived from document D4 alone or in combination with any of the other prior-art documents D1, D11, D29 and D33 invoked by the appellant as supplementary documents.

5.11.1 Both D4 and D33 concern a treatment with viable LGG and do not suggest using inactivated LGG. The appellant cited the following passage from D33:

"Whether a response occurs after treatment with live probiotic bacteria (28) vs DNA from heat-killed probiotics (29) remains under investigation."

But the context of this quote is a general discussion of prior scientific publications, none of which concerns LGG (see D33: page 551, column 1, second paragraph).

Reference (28) concerns viable *Lactobacillus reuteri* bacteria (see D33: page 552); reference (29), cited as D33A in the present proceedings, relates to DNA from various bacteria, none of which is LGG. Thus, the cited passage would not provide the person skilled in the art with any incentive to use heat-inactivated LGG for the treatment of systemic inflammation in an infant.

5.11.2 Document D1 relates to *in-vitro* data obtained with a cancer cell line (Caco-2 cells). The respondent argued, plausibly and in line with the cautionary statement in paragraph [0023] of document D4 (see point 5.3.2 above), that this was not an appropriate model for a therapy involving administration to human infants, since effects allegedly observed in a cancer cell-based assay could not necessarily be extrapolated to effects in multicellular organisms, let alone human infants. The appellant did not provide any verifiable corroboration for its counter-argument that, since the cell lines were identical in adults and infants, the

experimental model used in document D1 was equally valid for adult and infant cells. Document D1 itself does not discuss or suggest a potential application to human infants. In these circumstances, it is not possible to infer conclusively from the information provided in document D1 that heat-inactivated LGG material may be useful in the treatment of systemic inflammation in infants or provide an improved therapeutic benefit in comparison with viable LGG.

5.11.3 As set out above in the context of the assessment of novelty (see section 4 above), while document D11 relates to inactivated probiotic bacteria in general, it does not specifically disclose or discuss the administration of heat-inactivated LGG to infants, let alone with the aim of treating systemic inflammation. The experimental data provided in D11 were obtained with a bacteria mix not containing any strain of *Lactobacillus rhamnosus* (see D11: example 1). Thus, D11 does not provide any focused teaching which could direct the person skilled in the art to the subject-matter of claims 1 or 12.

5.11.4 According to document D29, the anti-inflammatory effect of viable or heat-inactivated LGG was assessed on two rat models of experimental arthritis. The appellant no longer contested that ten-week old rats (as used in D29) are young adult rats rather than infant rats. D29 does not discuss the administration of LGG to infant rats or human infants. Also, no teaching can be found in D29 that the effect of LGG on systemic inflammation can be improved by heat inactivation. For these reasons, the information presented in D29 cannot lead to the claimed subject-matter as the solution to the objective technical problem.

5.11.5 Document D31 (entitled: "Probiotic Bacteria in the Management of Atopic Disease: Underscoring the Importance of Viability") reports the finding, from a study carried out with human infants, that treatment with heat-inactivated LGG was associated with adverse gastrointestinal symptoms and diarrhoea. D31 concludes that the adverse symptoms observed question the use of non-viable probiotics for infant therapy in general (see D31: abstract and page 226, column 1, at the bottom, and point 5.14 below). Thus, D31 actually explicitly teaches away from employing heat-inactivated LGG.

5.12 For these reasons, the subject-matter of claims 1 and 12 involves an inventive step starting from the teaching of document D4.

Inventive-step assessment starting from D33

5.13 The assessment of inventive step starting from the teaching of document D33 is, in fact, identical to the assessment starting from the teaching of document D4 presented in points 5.6 to 5.12 above, and the same conclusion is reached since D33 does not introduce any new aspects.

Inventive-step assessment starting from D31

5.14 Document D31 discloses data obtained in a study with human infants involving a mean intake of 3×10^{10} cfu per kg body weight of LGG (thus, higher than the upper limit of 1×10^{10} defined in claims 1 and 12) in viable or inactivated freeze-dried form *versus* placebo. D31 reports that atopic eczema improved significantly in all treatment groups (including placebo) but that the treatment with heat-inactivated LGG was associated with adverse gastrointestinal symptoms and diarrhoea, while no adverse reactions were reported in the groups

receiving placebo or viable LGG. Based on these observations, D31 draws the conclusion that the supplementation of infant formulas with viable, but expressly not with heat-inactivated, LGG is a potential approach for the management of atopic eczema and cow's milk allergy. According to D31, the adverse gastrointestinal symptoms observed question the use of non-viable probiotics for infant therapy in general (see D31: abstract and page 226, column 1, last paragraph, and point 5.11.5 above).

No evidence is on file showing a particular technical effect associated with the lower dosage range defined in claims 1 and 12.

Based on experimental data obtained in a clinical study with human infants, document D31 recommends the administration of viable LGG. The administration of heat-inactivated LGG was also examined as a possible alternative but is expressly not recommended in D31. This teaching is not altered by the fact that D31 speculates about possible reasons for the adverse effects (see D31: page 226, column 1, lines 1 to 21). Also, it cannot be derived from the information presented in D31 that the treatment with heat-inactivated LGG (irrespective of adverse effects) had a better efficacy than the treatment with placebo or viable LGG (see D31: Figure 1). Thus the teaching of document D31 cannot lead to the claimed subject-matter.

Conclusion

5.15 For these reasons, the subject-matter defined in claims 1 and 12 of the main request involves an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

D. Hampe A. Lindner

Decision electronically authenticated